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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/919,501	08/28/97	O'GORMAN S	SALK2190

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EXAMINER	
WILSON,M	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/14/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/919,501	Applicant(s) O'Gorman et al
	Examiner Wilson, Michael C.	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-45* is/are pending in the application.

Of the above, claim(s) *3, 17, and 45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4-16, and 18-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Information Disclosure Statement filed Jan. 28, 1998 has been considered and made of record.

Applicant is reminded of the proper language and format for an abstract of the disclosure (See MPEP § 608.01(b)).

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

The abstract should be amended so as to contain less than 250 words.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1, 2, 4-16 and 18-44, drawn to methods of making transgenic animals, classified in class 800, subclass 21.

   II. Claims 1, 3-8, 10-11, 17-22, 24-27 and 45, drawn to methods of making transgenic plants, classified in class 800, subclass 278.

2. The inventions are distinct, each from the other because of the following reasons: Inventions of Group I and Group II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not used together, have different modes of operation and different functions. The materials and protocols used to make transgenic plants are materially distinct and separate from those used to make transgenic plants. In addition, transgenic plants have separate uses from transgenic animals as transgenic animals can be used as models for human disease whereas transgenic plants cannot. Transgenic plants are not required to use transgenic animals.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

4. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Stephen E. Reiter on Nov. 23, 1998, a provisional election was made with traverse to prosecute the invention of Group I, claims 1, 2, 4-

16 and 18-44. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3, 17 and 45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a nucleic acid construct comprising a mouse protamine 1 promoter operatively linked to Cre recombinase, 2) mouse embryonic stem cells comprising said nucleic acid constructs, 3) a method of making said embryonic cells, 4) a method of making ES cells wherein recombination of a second marker gene occurs comprising obtaining a male mouse whose genome comprises a nucleic acid construct comprising a mouse protamine 1 promoter operatively linked

to Cre recombinase wherein expression of Cre recombinase occurs in the sperm, heart and spleen, breeding said male mouse to a female mouse whose genome comprises a marker gene construct comprising a first marker gene flanked by loxP target sites wherein said first marker gene is inserted between the promoter and the coding region of a second marker gene that is not expressed, obtaining second generation ES cells from such a breeding wherein recombination of the marker gene construct occurs and 5) a method of making ES cells wherein recombination of a second marker gene occurs comprising obtaining a male mouse whose genome comprises a nucleic acid construct comprising a mouse protamine 1 promoter operatively linked to Cre recombinase wherein expression of Cre recombinase occurs in the sperm, heart and spleen, breeding said male mouse to a wild-type female mouse, obtaining ES cells, transfecting said ES cells with a marker gene construct comprising a first marker gene flanked by loxP target sites wherein said first marker gene is inserted between the promoter and the coding region of a second marker gene that is not expressed wherein recombination of the marker gene construct occurs, does not reasonably provide enablement for 1) a nucleic acid construct comprising a germline-specific promoter operatively associated with recombinase coding sequence, 2) an embryonic stem cell comprising said nucleic acid construct, 3) a method for excision of the selectable marker from ES cells comprising a selectable marker flanked by two recombination target sites, 4) a method of producing recombinant alleles comprising introducing a nucleic acid fragment flanked by two recombination target sites into ES cells and passaging the genome derived from said embryonic stem cells through gametogenesis or 5) a method of generating recombinant livestock.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification is directed toward a nucleic acid construct expressing the recombinase gene for the purpose of conditionally expressing a gene of interest in ES cells. The ES cells can be used to make mice in which recombinase is expressed in gametes such that the "marker gene would be excised in at least some of the progeny of ES cell chimeras" (page 3, line 3) or to "deliver recombined target nucleic acid constructs to the early embryo" (page 3, line 13). As the purpose of the specification is to guide the artisan on the making and using of the claimed invention, the artisan reads the claims in light of the teachings in the specification. The artisan reading the claimed invention in view of the specification regarding using the invention would only determine the use of nucleic acid constructs encoding recombinase for the purpose of creating transgenic animals. If the Applicants feels other uses for the method are disclosed in the specification, then the applicants should point to such uses by page and line number. Otherwise, the field of the present invention is nucleic acid constructs comprising a recombinase gene and ES cells comprising said nucleic acid construct for the purpose of delivering recombined target nucleic acid constructs to the early embryo and making transgenic animals.

The specification discloses the production of a nucleic acid construct comprising Cre recombinase operatively linked to the mouse protamine 1 (MP1) promoter (page 19, line 25) used to create transgenic mice (ProCre) (page 21, line 3). ProCre transgenic mice were bred with

transgenic mice containing a nucleic acid construct comprising a loxP-flanked neomycin resistance gene and the β-gal gene disrupting the RNA polymerase II locus (P2Bc, Figure 1, see also page 22, line 10). ProCre/P2Bc male mice were bred with wild-type female mice resulting a majority of embryos carrying a recombined P2Bc gene, namely P2Br (page 22, line 30). Note that the specification refers to the results of the experiment in Table 1 on page 22, line 30; however, Table 1 is not present in the instant application. Heterozygous ProCre/P2Bc male mice demonstrated expression of the recombined P2Bc (P2Br) in testes but not in kidney, brain or spleen when tested by Southern Blot analysis; however, only one other tissue beside testes was tested in each mice (page 23, line 30) and a more sensitive PCR analysis demonstrated ectopic recombinase activity in the heart, brain and spleen (page 24, line 32; page 25, lines 8-13). The state of the art at the time of filing was such that transgene behavior was unpredictable because transgene expression often occurs in unintended tissues or at developmentally incorrect times (Wall et al., 1997, J. Dairy Science, Vol. 80, pages 2213-2224; see page 2216, column 1, "Transgene expression"). The transgene may even be expressed but not functional (i.e. "silenced") (Mullins et al. 1996, J. Clin. Invest., Vol. 98, pages S37-S40; see page S37, column 2, line 7). The specification does not overcome the unpredictability in the art because the specification does not demonstrate or provide adequate guidance to obtain functional expression of a gene of interest and because the recombinase gene in the instant application is expressed in the heart, brain, spleen and sperm. The specification does not enable the use of the nucleic acids or the embryonic stem (ES) cells as claimed because the specification does not demonstrate functional expression of any gene, does

not correlate the expression of a marker gene to functional expression of any gene, provide a use for ES cells or mice expressing a non-functional marker gene or correlate ES cells or mice expressing a functional marker gene to ES cells or mice expressing other genes that may be of use. The production of a ProCre mouse (page 21) alone is not of use because it does not have a phenotype that distinguishes it from the wild-type mouse. The production of a ProCre/P2Bc mouse alone is not of use because it is not clear the recombined P2Bc is functional in any tissue, because expression of P2Br occurs in the heart, spleen, brain and testes, and because expression of a marker gene is not of apparent use as disclosed in the specification.

Overall, the phenotypes of the ES cells or transgenic mice of the instant application are not different than the phenotype of wild-type mice. The state of the art at the time of filing was such that if germline-specific recombinase activity were not sufficiently high to mediate recombination, the embryos would be mosaic and not display a mutant phenotype (Lewandoski et al. 1997, Current Biology, Vol. 7, pages 148-151; see page 151, column 1, line 4). Furthermore, the phenotype of transgenic animals is unpredictable due to the unpredictability of transgene expression (Mullins et al. 1996, J. Clin. Invest., Vol. 98, pages S37-S40; see page S37, column 2, line 7). The specification does not overcome the unpredictability in the art because it does not demonstrate an ES cell or mouse with a mutant phenotype that differs from the wild-type phenotype or provide adequate guidance to determine the expected phenotype with a reasonable expectation of success. The specification does not disclose a useful phenotype of an ES cell or a mouse obtained from an ES cell expressing functional a marker gene or any gene. As an example,

it is unclear whether a ProCre mouse crossed with a mouse bearing a target gene such as hoxb-1 would produce an ES cell or mouse with an useful phenotype because tissue specificity of the recombinase may vary, because expression of recombinase in heart tissue may adversely effect the phenotype of such an ES cell or mouse. The expression of recombinase in the heart of a ProCre/hoxb-1 mouse may allow expression of hoxb-1 in the heart and result in an undesirable phenotype or even death. The specification does not correlate the results obtained with the β-gal gene construct with the hoxb-1 gene construct such that one of skill would have a reasonable expectation of obtaining functional expression of hoxb-1 in an ES cell or a transgenic mouse. It would require undue experimentation for one of skill in the art at the time the invention was made to determine the expected phenotype that is of use in ES cells or mice resulting from the nucleic acids, embryonic stem cells and methods claimed using marker genes or any other genes.

The specification contemplates creating an embryo bearing a genetically lethal allele (page 4, line 18); however, the specification does not teach what genes to use or how to prevent death during embryonic stages. While it may be possible to obtain a mouse or ES cell bearing a non-functional lethal allele interrupted by a marker gene flanked by loxP targeting sites, the specification does not disclose a phenotype or use of an ES cell or mouse bearing a non-functional lethal gene. A male mouse wherein recombination and functional expression of the lethal gene occurs could be used to fertilize a wild-type egg which then would form a zygote expressing the lethal gene. However, it is unclear that this mouse can be obtained because it expresses a lethal gene in the embryo and would not come to term. The specification does not overcome the

unpredictability of the art because the specification does not disclose obtaining an ES cell or mouse bearing a functional lethal gene or correlate the results obtained using the P2Bc/r gene to lethal genes such that one of skill would have a reasonable expectation of success in obtaining a mouse that is of use.

Claims 12-16 and 18-44 are directed toward **any** embryonic stem cells and methods of using embryonic stem cells; however, the specification discloses only the production of embryonic stem cells from mice. The state of the art at the time of filing was such that a number of significant limitation regarding the production of non-mouse transgenic animals exist. For example, while the techniques used to create transgenic mice and rats are similar, female rats are superovulated in a narrow range of age and weight (Robl and Heideman, "Production of transgenic rats and rabbits," Transgenic animal technology, pages 265-270, 1994; see page 267, 4th paragraph through the end of the page). The specification does not teach how to superovulate female rats. Applicants claim methods of making transgenic livestock (claim 44); however, the state of the art at the time of filing was such that transgene expression and the physiological result of such expression in livestock is not always accurately predicted in transgenic mice (Wall, 1996, Theriogenology, Vol. 45, pages 57-68; page 62, line 7). The specification fails overcome the unpredictability in the art because the applicants do not correlate the results of transgenic mice with any other species such that one of skill in the art would be able to grow any embryonic cell, transfer DNA to any such cell or obtain germline transmission of transgenic

material in species other than mice. The specification does not provide adequate guidance such that transgenic animals other than mice can be obtained with a reasonable expectation of success.

The specification does not enable the production of nucleic acid constructs, embryonic stem cells or methods of using said nucleic acids or ES cells using any promoter, any recombinase or any recombination target sites. It is not clear that the protamine 1 gene promoter has the same specificity as the protamine 2 gene promoter. It is also not clear that the FLP recombinase or R gene product of *Zygosaccharomyces* would be integrated into the genome in such a way as to be able to mediate recombination in embryonic stem cells because transgene expression is unpredictable (Mullins et al. 1996, J. Clin. Invest., Vol. 98, pages S37-S40; see page S37, column 2, line 7). The specification also does not disclose any other recombination target sites other than loxP target sites flanking a marker gene. It would require undue experimentation for one of skill to determine which promoters, recombination target sites or genes of interest can be used other than mouse protamine 1, loxP and Cre recombinase to obtain a mouse with a phenotype that differs from the wild-type wherein germline-specific expression of a gene occurs.

Thus, in view of the breadth of the claims, the amount of experimentation required to determine how to use ES cells or mice expressing non-functional gene, how to determine the phenotype of interest, how to use ProCre mice alone, the unpredictable state of the art at the time of filing, the lack of guidance in the specification as to how to make any ES cell or transgenic animal other than mice using any genes other than the mouse protamine 1 promoter operatively linked to the Cre recombinase gene or using any recombination target sites other than loxP target

sites, and the lack of working examples, it would have required undue experimentation for one skilled in the art to make and use the claimed invention without a reasonable expectation of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 33, 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "essential" in claim 33 is indefinite because it is not defined in the specification and may have various meanings in the art.

The phrase "recombinase responsive construct" in claim 40 is indefinite because it is not defined in the specification and does not have a meaning in the art.

In claim 10, the term "conditional promoter" is indefinite because the term is not defined in the specification and may have various meanings in the art. It is unclear whether the applicants consider MP1 promoter a conditional promoter because it promotes expression of gene only in sperm tissue conditions or whether the applicants intend to claim some other condition required for expression.

In claim 13, the term "recombination target sites" is indefinite because the term is not defined in the specification. It is unclear whether applicants intend to include endonuclease cut sites as recombination target sites.

In claim 44, the term "pluripotential" is indefinite because the term is not defined in the specification and may have various meanings in the art. It is not clear whether the applicants consider pluripotent ES cell to have two potential routes of differentiation or twenty potential routs of differentiation. The term "livestock" is also indefinite because the term is not defined in the specification and the term may have various meanings in the art. It is not clear whether the applicant consider mice livestock as the only animal disclosed in the specification is a mouse.

Claims 28-44 are unclear because they do not result in a step wherein the desired endpoint is obtained such as obtaining ES cells or transgenic mice with a desired phenotype or functional expression of a gene occurs.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-2 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Lewandoski et al. (1997, Current Biology, Vol. 7, pages 148-151).

Lewandoski et al. teach the production of a nucleic acid construct comprising the ZP3 promoter operatively linked to the Cre recombinase gene (page 148, column 1, line 1).

Lewandoski et al. clearly anticipate all the limitations of the claims as ZP3 is a germline-specific promoter.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-2, 4-5, 10-16 and 18-19, 24-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. (1994, Science, Vol. 265, pages 103-106) in view of Zambrowicz et al. (1994, Biology of Reproduction, Vol. 50, pages 65-72) and Lakso et al. (June 1996, Proc. Natl. Acad. Sci., Vol. 93, pages 5860-5865).

Gu et al. teach the production of nucleic acid constructs comprising a T-cell specific promoter operatively linked to Cre recombinase, ES cells comprising such a construct, a method of excising a selectable marker from ES cells and a method of producing recombined alleles (page 104, column 1, line 18; page 104, Figure 1; see in particular page 105, column 2, line 17 through the end of the page). Gu et al. do not teach the production of a nucleic acid construct comprising a germline-specific promoter or ES cells comprising a nucleic acid construct comprising a germline-specific promoter operatively linked to a Cre recombinase gene.

However, at the time of filing, Zambrowicz et al. teach the mouse protamine-1 (MP1) promoter can be used to obtain sperm-specific expression of genes (page 65, column 2, line 15) and contains a Cre-like sequence which regulates sperm-specific transcription (page 71, column 2, line 23).

Thus, it would have been obvious to replace the T-cell specific promoter used in the Cre-loxP system taught by Gu et al. with the MP1 promoter taught Zambrowicz et al. to obtain sperm-specific expression of Cre recombinase. One of skill would have been motivated to combine the Cre-loxP system and the MP1 promoter to eliminate *in vitro* ES cell manipulation to obtain germ-line transmission of a recombined transgene. Motivation to combine is provided by Lakso et al. who state the need to obviate the extended culture of ES cells in order to expose the ES cells to recombination by directing recombination to the embryo (page 5865, column 1, first full paragraph). As a sperm-specific promoter operatively linked to Cre recombinase would produce sperm in which recombination occurs then used to fertilize eggs and obtain recombined embryos, thus obviating the extended culture and genetic manipulation of ES cells to obtain the same thing. The limitation of recombination target sites is obvious in view of the term loxP target sites taught by Gu et al. The limitations of gametogenesis in claim 28, spermatogenesis in claim 29, and oogenesis in claim 30 are obvious in view of the breeding approach taught by Gu et al. (page 104, Figure 1) because the genome of ES cells is passaged through spermatogenesis or oogenesis. The limitation of site specific-mediated recombination in claim 34 is obvious in view of the T-cell-specific mediated recombination obtained by Gu et al. The term conditional

promoter (claim 36 and elsewhere) is obvious in view of the teaching of the MP1 promoter as the term is not defined in the specification and may have various meanings in the art. The limitation of a second nucleic acid construct in claim 36 is obvious in view of Gu et al. by teaching an ES cell with the recombinase gene construct and the marker gene construct. The limitation of livestock in claim 44 is obvious in view of Gu et al. by teaching mice which can be considered livestock as they are kept or raised for use. One of skill would have had a reasonable expectation in obtaining ES cell expressing a marker gene using the Cre recombinase system and the MP1 promoter.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

14. Claims 1, 6-9 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. (1994, Science, Vol. 265, pages 103-106) in view of Zambrowicz et al. (1994, Biology of reproduction, Vol. 50, pages 65-72) and Lakso et al. (June 1996, Proc. Natl. Acad. Sci., Vol. 93, pages 5860-5865) as applied to claims 1-2, 4-5, 10-16 and 18-19, 24-29, 31-44 above, and further in view of Onouchi et al. (1995, Mol. Gen. Genet., Vol. 247, pages 653-660).

The combined teachings of Gu et al., Zambrowicz et al. and Lakso et al. teach the production of a nucleic acid construct comprising a MP1 sperm-specific promoter operatively linked to a Cre recombinase gene and ES cells comprising such nucleic acid constructs. Gu et al. teach the production of nucleic acid constructs comprising a T-cell specific promoter operatively linked to Cre recombinase, ES cells comprising such a construct, a method of excising a selectable

marker from ES cells a: a method of producing recombined alleles (page 104, column 1, line 18; page 104, Figure 1; see i particular page 105, column 2, line 17 through the end of the page). Zambrowicz et al. teac .he mouse protamine-1 (MP1) promoter can be used to obtain sperm-specific expression of g nes (page 65, column 2, line 15). Motivation to combine is provided by Lakso et al. who state t need to obviate the extended culture of ES cells in order to expose the ES cells to recombinati by directing recombination to the embryo (page 5865, column 1, first full paragraph). The co bined teachings of Gu et al., Zambrowicz et al. and Lakso et al. do not teach the production o nucleic acid construct comprising FLP recombinase or the R gene product of *Zygosaccha myces*.

However, at the me of filing Onouchi et al. disclose the FLP recombinase system and the R gene product of *Zyg ccharomyces* system (page 653, column 2, line 8-13).

Thus, it would ve been obvious to replace the Cre recombinase gene with the FLP recombinase gene or th R gene product of *Zygosaccharomyces* taught by Onouchi et al. Motivation is provided y Onouchi et al. by stating the Cre-lox, FLP-FRT and R-RS system are all similar and cause re mbination (page 653, column 2 , line 9). One of skill would have had a reasonable expectation success using the FLP-FRT or R-RS system and the MP1 promoter to obtain expression of a rker gene.

Thus, Applica claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to e contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson
December 4, 1998

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 1630